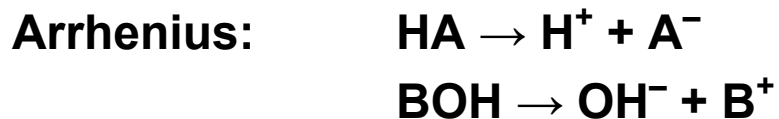# KONSTANTA DISOCIACIJE, IONIZACIJSKA KONSTANTA

Definicija kisline oz. baze:

Arrhenius: $\qquad$ $HA \rightarrow H^+ + A^-$

$\qquad\qquad\qquad$ $BOH \rightarrow OH^- + B^+$

Brönsted-Lowry:

$\qquad\qquad$ $HCl + H_2O \rightarrow H_3O^+ + Cl^-$

$\qquad\qquad$ kisl.1 $\quad$ baza2 $\quad$ kisl.2 $\quad$ baza1

Lewis: $\qquad\qquad$ $H^+ + :NH_3 \rightarrow NH_4^+$

$\qquad\qquad\qquad\qquad$ baza

$\qquad\qquad$ $Cl_3B + :O(CH_3)_2 = Cl_3B:O(CH_3)_2$

$\qquad\qquad$ kisl. $\qquad$ baza
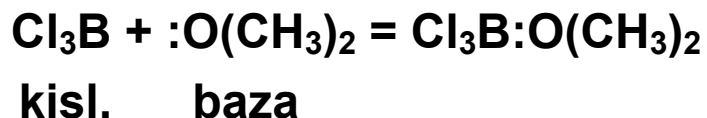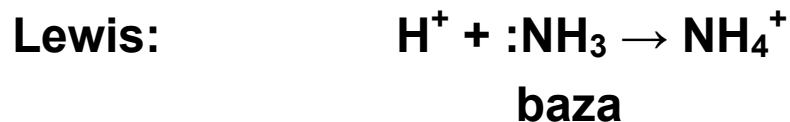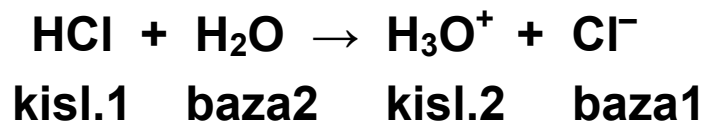
Določanje pK_a:

- potenciometrična titracija (pH merimo)

za območje 2,0 < pK_a < 11 (netočnost steklene elektrode)

- spektrofotometrične metode:

Beerov zakon: $A = A_i + A_M$

analitska λ

Frakcija $F_i = \dfrac{[A^-]}{[A^-] + [HA]}$

$$F_M = \dfrac{[HA]}{[A^-] + [HA]}$$

$A_i = \varepsilon_1 \cdot F_I \cdot c_{tot} \cdot I$
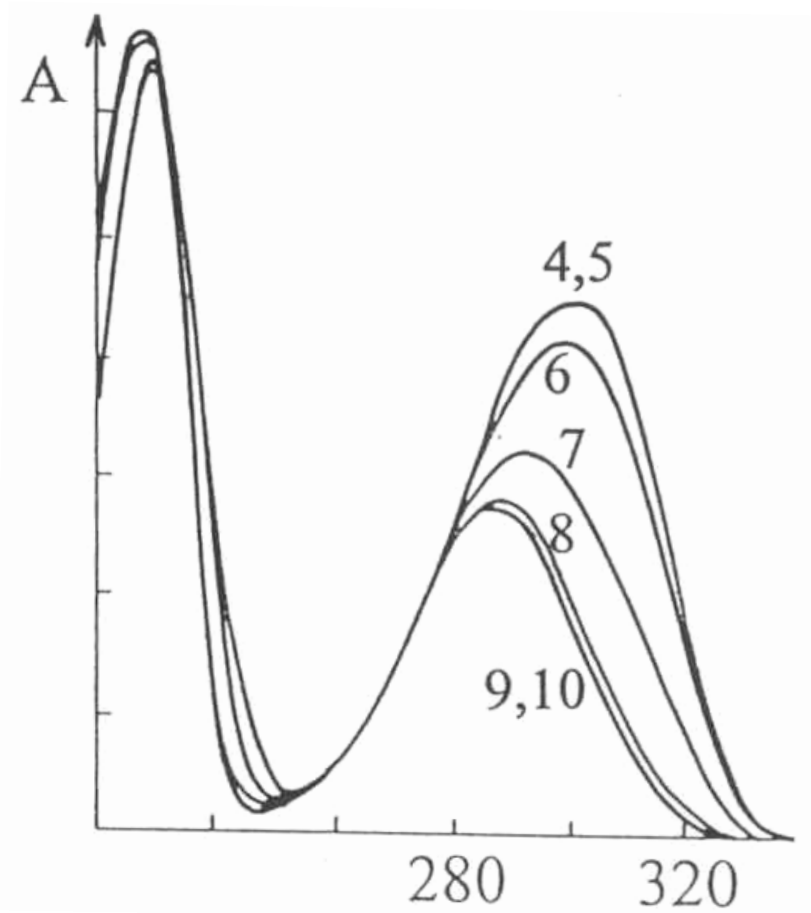
$A_M = \varepsilon_2 \cdot F_M \cdot c_{tot} \cdot I$

Table 1: Chromophore structures

Chromophore	System	λ_{max} (nm)	Molar extinction (ε)
Benzene		184	46700
Naphtalene		220	112000
Anthracene		252	199000
Pyridine		174	80000
Quinoline		227	37000
Ethylene	C = C	190	8000
Acetylide	C ≡ C	175 – 180	6000
Ketone	C = O	195	1000
Thioketone	C = S	205	Strong
Nitrile	C ≡ N	160	–
Nitroso	N = O	302	100
Nitro	NO_2	210	Strong
Amino	NH_2	195	2800
Thiol	SH	195	1400
Halide	Br, etc.	208	300

Table 2: Chromophore behaviour in an homologous series (C_6H_5–R) at > 190 nm

Substituent	λ_{max} (nm)	Molar extinction (ε)
H	203,5	7400
CH_3	206,5	7000
Cl	209,5	7400
OH	210,5	6200
OCH_3	217	6400
CN	224	13000
COO^-	224	8700
COOH	230	11600
NH_2	230	8600
$NHCOCH_3$	238	10500
$COCH_3$	245,5	9800
NO_2	268,5	7800

$$F_i = K_a / \left([H^+] + K_a\right) \qquad F_i = \frac{1}{1 + [H^+]/K_a} \left(\frac{[HA]}{[A^-]} = \frac{[H^+]}{K_a}\right)$$

$$F_m = [H^+] / \left([H^+] + K_a\right) \qquad F_m = \frac{1}{1 + [A^-]/HA} \left(\frac{[A^-]}{HA} = \frac{K_a}{[H^+]}\right)$$

A = ($\varepsilon_l \cdot F_l + \varepsilon_m \cdot F_m$) c$_{tot}$; ista celica, l = konst.

ker je: ε = A / c $\rightarrow$

$$\varepsilon = \frac{\varepsilon_l K_a}{[H^+] + K_a} + \frac{\varepsilon_M [H^+]}{[H^+] + K_a} \quad \textbf{če je c}_{tot} \textbf{ = konst. } \rightarrow$$

$$A = \frac{A_i K_a}{[H^+] + K_a} + \frac{A_M [H^+]}{[H^+] + K_a}$$

$$A[H^+] + A K_a = A_i K_a + A_M [H^+]$$

$$A K_a - A_i K_a = A_M [H^+] - A[H^+]$$

$$K_a = \frac{[H^+][A_M - A]}{A - A_i}$$

$$pK_a = pH + \log \frac{A - A_i}{A_M - A} \qquad \text{za kisline}$$

$$pK_a = pH + \log \frac{A_M - A}{A - A_i} \qquad \text{za baze}$$

- metoda topnosti (fazna ravnotežja) – logP:

$$S_0' = [HA] + [A^-] \qquad [A^-] = \frac{K_a[HA]}{[H^+]} \Rightarrow \quad S_0' = [HA] + \left(K_a[HA] \right)/[H^+] \Rightarrow$$

$$S_0' = S_i \left(1 + 10^{pH - pK_a} \right)$$

S_0' – določena topnost pri nekem pH

S_i – intrinzična topnost

$$pK_a = pH - \log\left(\frac{S_0'}{S_i} - 1\right)$$ **za kisline**

$$pK_a = pH + \log\left(\frac{S_0'}{S_i} - 1\right)$$ **za baze**

- konduktometrija:

stopnja ionizacije $\quad \alpha = \dfrac{\Lambda_c}{\Lambda_\infty}$

Λ_c **– ekvivalentna (molarna) prevodnost pri neki koncentraciji**

Λ_∞ **– ekvivalentna (molarna) prevodnost pri neskončnem razredčenju, uporabna za zelo šibke kisline, $pK_a \approx 11 - 14$**

$$K_a = \frac{\alpha^2 c}{1 - \alpha}$$

- ostale metode: Raman spektrometrija, NMR, termometrične metode
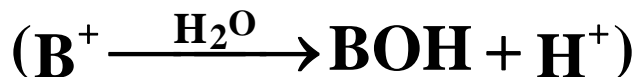
pK_a, IZRAČUNAN IZ PORAZDELITVENEGA KOEFICIENTA (P) – fazno ravnotežje

$$P = \frac{c_0}{c_w} = \frac{c_0}{[HA]} \qquad\qquad K_a = \frac{[H^+][A^-]}{[HA]} \Rightarrow \frac{K_a}{[H^+]} = \frac{[A^-]}{[HA]}$$

$$P_{nav} = \frac{c_0}{[HA]+[A^-]} \qquad\qquad \frac{P}{P_{nav}} = \frac{\cancel{c_0}([HA]+[A^-])}{[HA]\cancel{c_0}}$$

$$P = P_{nav}\left(1 + \frac{[A^-]}{[HA]}\right) = P_{nav}\left(1 + \frac{K_a}{[H^+]}\right) \quad \textbf{za kisline}$$

$$P = P_{nav}\left(1 + \frac{[H^+]}{K_a}\right) \quad \textbf{za baze}$$

$$(B^+ \xrightarrow{\ H_2O\ } BOH + H^+)$$

Enačbe za linearno regresijo:

y = n + k · x

$$\frac{1}{P_{nav}} = \frac{1}{P} + \frac{K_a}{P} \cdot \frac{1}{[H^+]} \qquad \textbf{za kisline}$$

$$\frac{1}{P_{nav}} = \frac{1}{P} + \frac{1}{P \cdot K_a} \cdot [H^+] \qquad \textbf{za baze}$$

pK_a, IZRAČUNAN IZ HPLC PARAMETROV

$$K_R = c_s / c_m = e^{-\left(\Delta G_R^0 / RT\right)}$$

K_R – ravnotežna konstanta, ki opisuje dinamično ravnotežje med stacionarno in mobilno fazo

ΔG_R^0 – standardna prosta entalpija za prehod spojine iz mobilne v stacionarno fazo

c_s, c_m – ravnotežni koncentraciji spojine v stacionarni in mobilni fazi

Retencijski kapacitivni faktor: $k' = (t_R - t_0) / t_0$

$$k' = \frac{k_n' + k_i' \cdot K_a / [H^+]}{1 + K_a / [H^+]} \quad \text{za kisline}$$

$$k' = \frac{k_n' + k_i' \cdot [H^+] / K_a}{1 + [H^+] / K_a} \quad \text{za baze}$$

k_n' in k_i' – kapacitivna faktorja molekularne (neionizirane) in ionizirane oblike

The ionisation properties of acyclovir and deoxyacyclovir

A. Kristl, A. Mrhar and F. Kozjek

Department of Pharmacy, Faculty of Natural Sciences and Technology, University in Ljubljana, Ljubljana (Slovenia)

Figure 1:

Absorbances of N_2AcACV in buffer solutions at various pH, in 0.5 and 1 M HCl and in 0.5 and 1 M NaOH at two different wavelenghts.
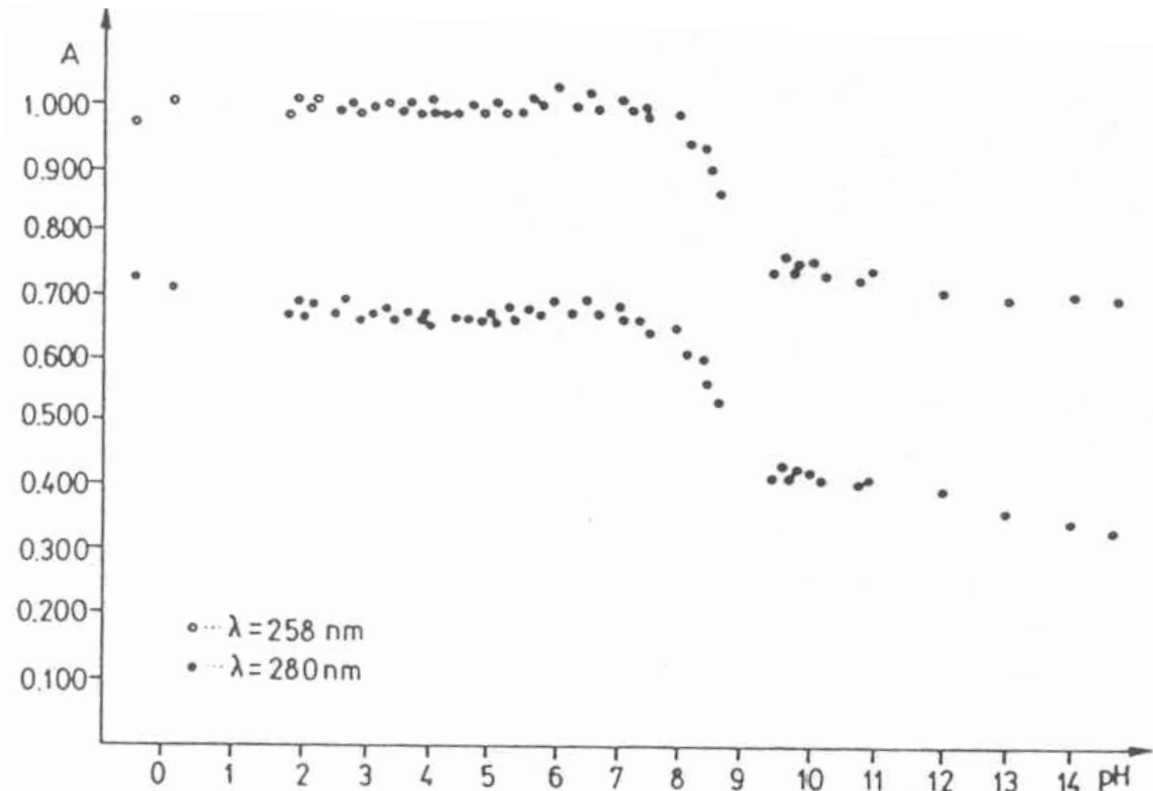
Table 3: Absorbances of N$_2$AcACV solutions in buffers ranging from pH 7,27 to 9,81 and in 1 M HCl and 1 M NaOH at different wavelenghts.

pH	A$_{259,6}$	A$_{259,8}$	A$_{260,0}$	A$_{260,2}$	A$_{260,4}$
7,27	1,007	1,005	1,002	0,999	0,997
7,48	0,988	0,986	0,984	0,980	0,977
7,88	0,994	0,992	0,990	0,987	0,985
8,09	0,961	0,959	0,958	0,954	0,953
8,28	0,946	0,944	0,943	0,942	0,939
8,43	0,909	0,908	0,905	0,904	0,903
8,59	0,861	0,861	0,861	0,860	0,860
8,66	0,882	0,881	0,880	0,878	0,877
9,42	0,753	0,753	0,752	0,753	0,753
9,60	0,786	0,786	0,787	0,786	0,786
9,68	0,748	0,750	0,751	0,750	0,749
9,74	0,780	0,780	0,782	0,781	0,781
9,81	0,781	0,781	0,782	0,782	0,782
1M HCl	1,040	1,043	1,044	1,046	1,049
1M NaOH	0,730	0,730	0,730	0,729	0,729

$$pK_a = pH + \log \frac{A_i - A}{A - A_n}$$

y (under pK_a), x (under the fraction)
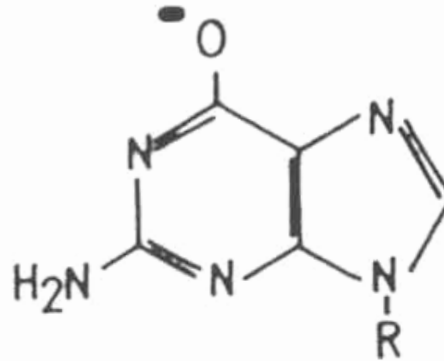
$pK_a = 8{,}54 \pm 0{,}03$

Figure 2: The predominant structures of protonated (a) and deprotonated (b) guanosine. R = D-ribofuranose
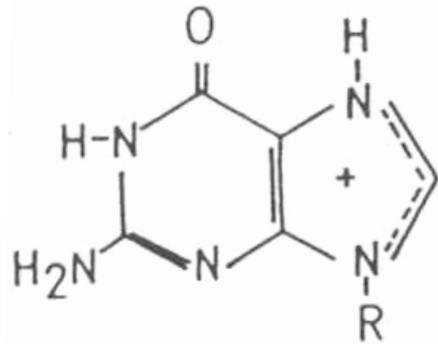
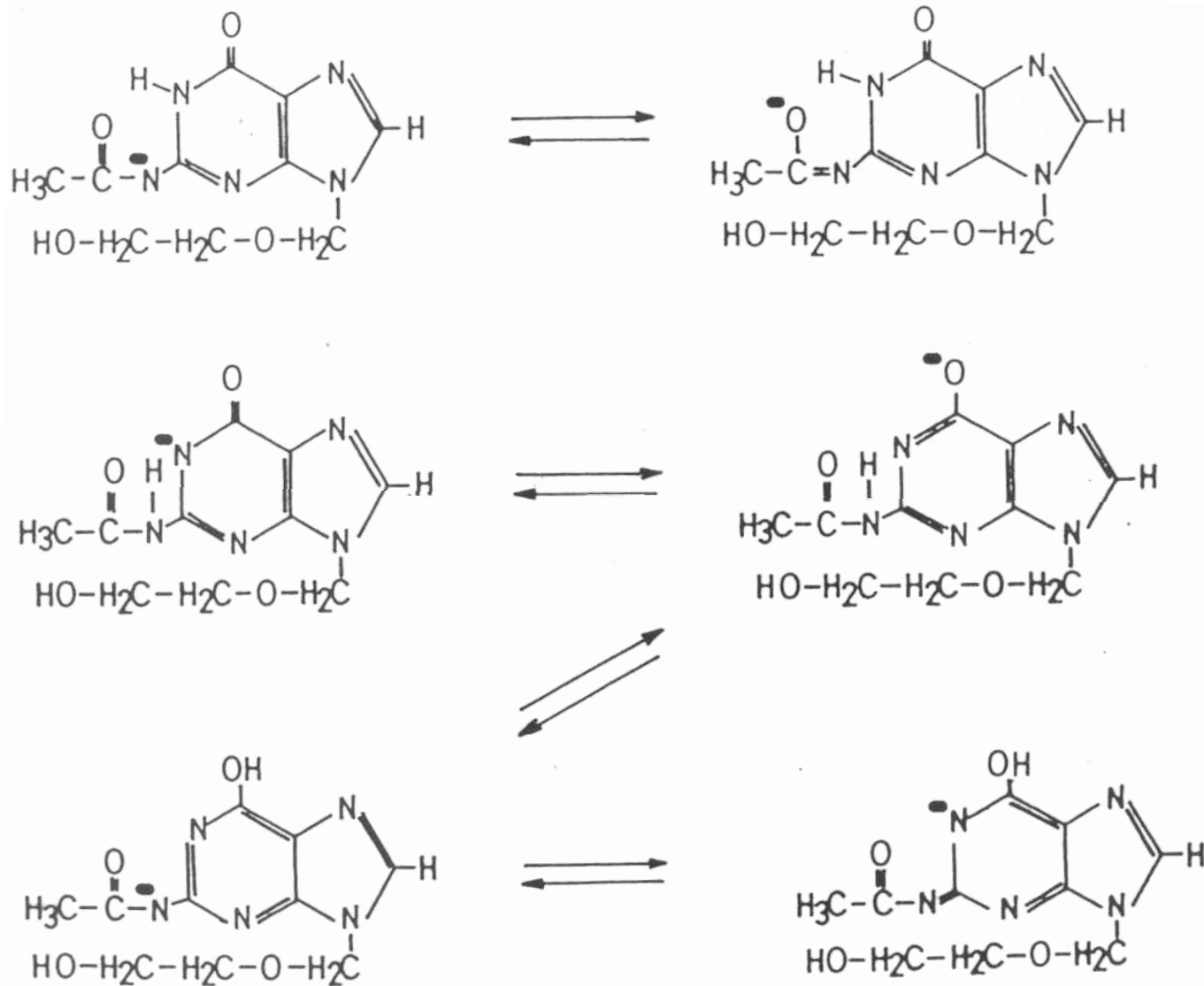a   b

Figure 3: Possible tautomeres of N₂AcACV.

Lipophilicity of guanine derivatives

A. Kristl [1], A. Mrhar [1], F. Kozjek [1] and J. Kobe [2]

*[1] Faculty of Natural Sciences, Department of Pharmacy, E. Kardelj University, Ljubljana (Yugoslavia)
and [2] Boris Kidrič Institute of Chemistry, Ljubljana and Pharmaceutical and Chemical Works, Krka (Yugoslavia)*

$$Pn = \frac{Apd - Apo}{Apo} \tag{1}$$

$$Pn = \frac{(Apd - Apo) \cdot Vv}{Apo \cdot Vo} \tag{2}$$

$$1/Pn = 1/P + (1/P \cdot Ka) \cdot H^+ \tag{3} \quad baze$$

$$1/Pn = 1/P + (Ka/P) \cdot 1/H^+ \tag{4} \quad ksl.$$

$$1/Pn = 44.22 \pm 12.43 + (11040.29 \pm 324.17) \cdot H^+ \tag{5}$$

$$1/Pn = 38.42 \pm 28.45$$

$$+ (2.24 \cdot E - 8 \pm 1.39 \cdot E - 9) \cdot 1/H^+ \tag{6}$$

and eq. (7) for DCV:

$$1/Pn = 10.40 \pm 1.08 + (44868.94 \pm 4123.90) \cdot H^+ \tag{7}$$

Table 4: Absorbances of ACV solutions before and after shaking with n–octanol and the calculated values of apparent partition coefficients.

pH	Apd	Apo	Pn
Ratio water/lipid phase 1:1			
1.48	0.412	0.411	0.0024
2.54	0.490	0.483	0.0145
3.55	0.499	0.490	0.0184
3.56	0.478	0.467	0.0235
5.54	0.467	0.461	0.0130
6.41	0.435	0.426	0.0211
6.50	0.455	0.445	0.0225
7.52	0.495	0.489	0.0123
Ratio water/lipid phase 1:2			
1.49	0.401	0.399	0.0025
3.56	0.478	0.457	0.0230
6.41	0.435	0.416	0.0228
9.55	0.382	0.374	0.0107
Ratio water/lipid phase 1:3			
3.56	0.478	0.452	0.0192
6.41	0.435	0.400	0.0292
7.53	0.502	0.478	0.0167
8.43	0.472	0.447	0.0186
Ratio water/lipid phase 1:4			
6.50	0.468	0.430	0.0221
7.53	0.502	0.462	0.0216
7.57	0.507	0.444	0.0355
8.43	0.472	0.429	0.0251
10.36	0.411	0.408	0.0018

Table 5: Absorbances of DCV solutions before and after shaking with n–octanol and the calculated values of apparent partition coefficinents.

pH	*Apd*	*Apo*	*Pn*
Ratio water/lipid phase 1:1			
5.55	0.324	0.297	0.0909
7.52	0.329	0.300	0.0967
9.46	0.256	0.232	0.1034
9.55	0.328	0.297	0.1044
Ratio water/lipid phase 1:2			
3.56	0.232	0.214	0.0421
6.42	0.343	0.283	0.1060
9.55	0.328	0.275	0.0964
Ratio water/lipid phase 1:3			
3.56	0.232	0.205	0.0439
6.42	0.343	0.264	0.0997
7.57	0.289	0.222	0.1006
8.44	0.334	0.260	0.0949
9.55	0.328	0.255	0.0954
10.36	0.359	0.279	0.0956
Ratio water/lipid phase 1:4			
5.58	0.326	0.240	0.0896
6.50	0.329	0.242	0.0899
7.53	0.316	0.226	0.0996
7.57	0.289	0.206	0.1007
8.44	0.334	0.244	0.0922
10.36	0.359	0.262	0.0926

The constants of ionization and their partition coefficients obtained from these equations are:

ACV: $pKa_1 = 2,41 \pm 0,27$; $pKa_2 = 9,06 \pm 0,88$; $logP = -1,615$ ($P = 0,024$)

DCV: $pKa = 3,63 \pm 0,085$; $logP = -1,02$ ($P = 0,096$)

From eq. (8), which represents the multiple least – squares linear regression method, another set of results for the constants of ionization and the partition coefficient for ACV was calculated.

$$1/P_n = 11087,12 \cdot H^+ + 2,21 \cdot E - 8 \cdot (1/H^+) + 45,46 \qquad (8)$$

where $pKa_1 = 2,39$; $pKa_2 = 9,31$; $logP = -1,657$ ($P = 0,022$).

$$1\big/ P_n = \frac{1}{P \cdot K_{a1}} \cdot [H^+] + \frac{K_{a2}(\text{acid})}{P} \cdot \frac{1}{[H^+]} + \frac{1}{P}$$

baza